Interferon-beta therapy induced minimal change disease: A case report.

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Abstract

Interferon-beta is recognized as first line treatment in relapsing remitting multiple sclerosis. Overall it is considered a safe drug; however, over the years there has been some concern on its effect on the kidneys. Here we present a case of nephrotic syndrome in a young lady suffering from relapsing remitting multiple sclerosis who had been on Interferon-beta-1a therapy for 8 months. Kidney biopsy was consistent with minimal change disease. The clinical condition started to improve gradually upon cessation of the Interferon therapy and concomitant treatment with prednisolone. The patient attained full and sustained remission after 8 weeks of therapy. This is the third documented case of minimal change disease secondary to therapy with Interferon-beta-1a. This case highlights the importance of regular urinary investigations during Interferon therapy.

Keywords: Nephrotic syndrome, Proteinuria, Hypoalbuminaemia, Acute kidney injury.

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Introduction

Multiple sclerosis is a chronic, demyelinating disease of the central nervous system, often leading to significant and progressive disability. Evidence suggests that Interferon-beta therapy decreases relapse rates and the formation of new demyelinating lesions in relapsing remitting and secondary progressive multiple sclerosis [1]. This drug is usually well-tolerated however side effects are relatively common. Documented effects include flu-like symptoms, injection site reactions and laboratory abnormalities such as lymphopenia, neutropenia, and raised liver transaminases [2]. Despite its relatively safe profile, isolated cases of nephrotic syndrome and less commonly glomerulonephritis have been reported in the literature. We hereby describe a case of minimal change nephrotic syndrome during treatment with Interferon-beta-1a in a patient with relapsing remitting multiple sclerosis, who attained full and sustained remission upon drug discontinuation and simultaneous steroid therapy.

Case Report

A 26 year-old lady was referred to hospital from a primary healthcare facility for investigation of a two day history of bilateral lower limb oedema, which she noticed primarily as difficulty in fastening her shoes. She was diagnosed with relapsing remitting multiple sclerosis 1 year previously, for which she was commenced on Interferon-beta-1a therapy at a dose of 30 mcg once weekly via the subcutaneous route. She had no other significant past medical history. Of note, she disclosed a family history of unspecified renal pathology in her late grandmother.

Physical examination was normal apart from non-pitting oedema of the lower legs bilaterally to the mid-shins. Initial investigations revealed normal electrolytes, serum urea and creatinine, normal liver panel but with significant hypoalbuminaemia at 25 g/L and elevated total cholesterol at 8.59 mmol/L. Total protein (49 g/L) and Immunoglobulin-G (4.2 g/L) were low but no paraprotein was detected. Urinalysis showed 3+ protein and low-grade haematuria (5-10 erythrocytes/high power field) without casts. Full quantification revealed approximately 8 g of proteinuria/day. Complete blood count, inflammatory markers, thyroid function tests, rheumatoid factor, anti-nuclear antibodies, extractable nuclear antigen, anti-double stranded DNA, anti-neutrophil cytoplasmic antibodies, complement levels, human immunodeficiency virus and hepatitis screen were within normal levels or negative. Chest X-ray, ECG and ultrasound scan of her kidneys were also normal.

Initial treatment included loop diuretics, angiotensin-converting enzyme inhibitor (up-titrated as tolerated), statin and discontinuation of the Interferon-beta-1a. A kidney biopsy was performed under ultrasound guidance. Light microscopy revealed no morphological abnormalities (Figure 1), whilst immunoperoxidase showed light mesangial staining for IgM and no staining for complement.

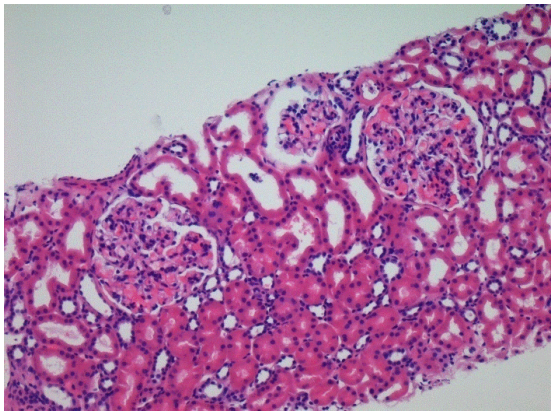

Figure 1. Normal kidney histology under light microscope (Hematoxylin and Eosin, low power magnification).

Electron microscopy revealed extensive podocyte foot process effacement, normal capillary loop basement membrane, endothelial layer, mesangium and absent electron-dense deposits, consistent with minimal change disease (Figure 2).

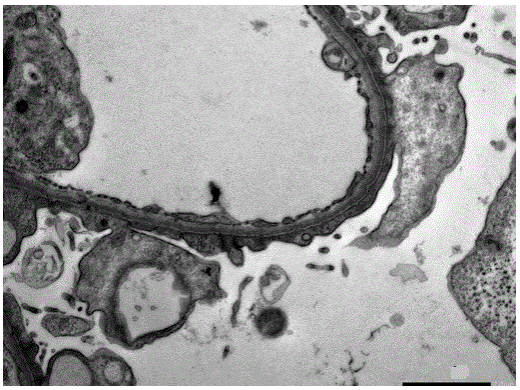

Figure 2. Electron microscope showing foot process effacement.

In view of this, the patient was started on prednisolone 60 mg once daily. Proteinuria decreased gradually until full remission was attained. In this case, 8 weeks of therapy were required until full remission, followed by a steroid taper over the next 4 months. No relapse was observed after 18 months of surveillance. Meantime, the Interferon-beta-1a was not restarted and Fingolimod was considered as a second line agent. Nonetheless, the patient refused to restart any immunotherapy in view of reasonable daily function, stable MRI appearance despite clinical relapses, and previous experience of side effects.

Discussion

Minimal Change Disease (MCD) is a type of podocyte disorder which accounts for over 90% of nephrotic syndrome in children, and 10-15% of cases in adults [3]. This group of podocyte disorders or podocytopathies encompass MCD, diffuse mesangial sclerosis, Focal Segmental Glomerulosclerosis (FSGS), and collapsing glomerulopathy [4]. Typical presentation includes nephrotic syndrome and Chronic Kidney Disease (CKD). In the case of MCD, the incidence of Acute Kidney Injury (AKI) in the adult population ranges between 20-25%, followed by complete resolution in the vast majority of cases [5-6]. It is thought that patients who develop CKD are more likely to have FSGS rather than MCD [6]. Our index case did not develop AKI or CKD at any stage of the disease. Microscopic haematuria can be present in 10-30% of adults with MCD [6-8]. Light microscopy examination typically shows no morphological abnormalities, albeit occasional mesangial prominence. Immunofluorescence is usually negative, although low-level staining with C3 and/or Immunoglobulin-M is occasionally seen. The hallmark of MCD is the podocyte foot effacement seen on electron microscopy without any electron dense deposits [9]. Although spontaneous remission is known to occur in MCD, this mostly happens in children. Moreover, long-standing untreated nephrotic syndrome can be associated with decrease in quality of life and significant morbidity such as thrombotic events, infections and accelerated arteriosclerosis [7-8,10-12]. Consequently, we opted for steroid therapy in the first instance as opposed to a watch and wait approach. Relapse in MCD is rather common especially in adults and some patients tend to develop steroid resistance [8]. This was not the case in our patient, presumably because the aetiology of podocyte injury had been eliminated. MCD has been linked to genetic abnormalities, infections, immunological factors, malignancy, metabolic disorders and drugs [4,13]. Indeed, several other drugs including gold, various antibiotics, non-steroidal anti-inflammatory drugs, oxazolidinedione anticonvulsants, lithium, interferon alpha, interferon gamma, methimazole, tamoxifen, enalapril, penicillamine, probenecid and certain immunizations have been implicated in the development of secondary MCD [14]. In this case, the temporal association between the initiation of Interferon therapy and the development of nephrotic syndrome suggests a direct association as opposed to a case of de-novo MCD.

Interferon-beta therapy is manufactured using recombinant DNA technology. Interferon-beta-1a is the native form and is produced using genetically engineered mammalian cells, whilst Interferon-beta-1b is the analogue molecule and is produced from genetically modified *Escherichia coli*. Interferon-beta-1b is non-glycocylated, has its terminal methionine deleted and cysteine at position-17 substituted for serine, intended to improve stability during storage [15-17]. The development of biopsy proven MCD secondary to Interferon-beta-1a therapy for the treatment of multiple sclerosis has been described in two other case reports. The first case was a 39 year old male who had been on Interferon-beta-1a therapy for 22 months before developing MCD with 6.7 g of proteinuria/day [18]. In this case, remission was attained within 6 weeks of drug discontinuation together with corticosteroid therapy. The second case describes a 44 year old female who had been on Interferon-beta-1a for 20 months prior to presentation [19]. Initially, she excreted 42 g of protein/day, decreasing to less than 1 g/day at 3 months of corticosteroid therapy and Interferon discontinuation. Looking at our index case and these two cases, one can appreciate the considerable variability in the severity of proteinuria and time interval between initiation of Interferon therapy and presentation. In all cases, management involved corticosteroid therapy together with Interferon withdrawal. Kumasaka and colleagues describe yet another

case of MCD in the setting of multiple sclerosis; however this time attributed to Interferon-beta-1b therapy [15]. The 43 year old lady had been on treatment for 21 months before developing proteinuria of 11 g/day. Again treatment was based on corticosteroids and cessation of Interferon. Interferon-beta therapy has been implicated in the development of other podocytopathies including FSGS [20-22] and membranous nephropathy [2], all cases presenting with nephrotic syndrome. In addition, some cases of direct endothelial injury have also been described in the literature, presenting with histological features of thrombotic microangiopathy [23-24] and immune complex mediated glomerulonephritis typically encountered in lupus nephritis [25].

The exact pathophysiological mechanism for the podocyte injury is still debated. It has been postulated that it may be a direct effect of the positively charged Interferon molecule which neutralises the anionic charge of the glomerular basement membrane and thus increasing its permeability [26]. Another mechanism could be related to the immunomodulatory effects induced by the Interferon therapy, whereby the cell mediated immunity is stimulated to produce cytokines and putative 'permeability factors' which interact with the podocyte and glomerular basement membrane leading to altered permeability. We tend to favour this alternative mechanism considering that MCD is associated with various causative factors, all of which could potentially alter the immune system and ultimately presenting with identical features of podocyte damage. From a clinical standpoint, the fact that MCD responds very well to immunosuppression also tends to support this mechanism.

Conclusion

Interferon-beta remains a useful therapy for multiple sclerosis provided that physicians are aware of the uncommon and yet possible adverse events. Our case describes one such renal complication in a young lady presenting with nephrotic syndrome secondary to MCD after 8 months of therapy. In view of this, we recommend augmented vigilance by employing regular urine investigations during Interferon-beta therapy. Any new onset proteinuria, especially if persistent, nephrotic range and/or associated with a rise in serum creatinine warrants further investigations and liaison with nephrologist. The prognosis of Interferon-beta induced nephrotic syndrome is excellent with corticosteroid therapy and Interferon discontinuation.

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

Research involving human participants

All procedures performed in this case report were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent was not required.

Informed consent

Informed consent was obtained from the index patient included in this case report.

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